REMARKS

Claims 1-2, 5, 7-15, 49, 56 and 57 were examined in the pending Office Action, the remaining claims having been cancelled or withdrawn as a result of a Restriction Requirement.

Claim 1 has been amended herein to remove embodiments (a) and (b), to indicate specific types of "binding" and to rearrange the part of the claim reciting various biologic activities. Support for the binding language and biological activity language can be found in the specification, for example at page 2, lines 23-28 and at page 16, line 13-25

Claim 2 is amended and also narrowed as a result of its dependence from claim 1.

Claims 8-10 are amended to insert "diagnostically useful" in front of "composition".

Claim 12 is amended to insert the term "labeled" in front of "polypeptide or peptide".

Claim 13 is amended to add a dependency to claim 12. [Any fee due for this extra claim is offset by the cancellation of claims 56 and 57 herein.

The scope of claim 49 has changed as a result of amendments to its parent claims 1 and 2.

Claims 56 and 57 are cancelled without prejudice or disclaimer.

Claims 1-2, 5, 7-15 and 49 are now active in this case. It is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. Applicants respectfully submit that their application is now in condition for allowance.

I. Withdrawal of Objections and Rejections

Applicants thank the Examiner for withdrawal of the previous objections or rejections as set forth in paragraphs 1-7 of the Action. In particular, rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Koide *et al.,* rejection of claims 1, 11, 13 and 49 under 35 USC § 102(b) as being anticipated by Borza *et al.* and rejection of claims 1, 5-15 and 49 under 35 U.S.C. 102(e) as anticipated by Simantov *et al.*. were all withdrawn in view of the amendments to the claims.

II. Claim Objections/Non-Art Rejections and Applicants Response

A. Claim 57 was objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants have cancelled claim 57.

B. Claims 1-2, 5, 7-15, 49 and 56-57 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite due to a typographical error - HGRP instead of HPRG. This has been either corrected or the claims cancelled, mooting this ground for rejection.

C. Claims 1-2, 5, 7-15, 49 and 56-57 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement

(1) In one case, this was a new matter rejection directed to a negative limitation, wherein applicants sought to remove from the scope of claim 1 *et seq.* the full-length human HPRG as defined by SEQ ID NO:1 or full-length rabbit HPRG as defined by SEQ ID NO:3. This language has been removed from the claims, thereby rendering moot this ground for rejection.

(2) The Office also asserted inadequate written support for the anti-angiogenic polypeptides (comprising the H/P domain of human or rabbit HPRG that are not the full-length human or rabbit HPRG) wherein the polypeptides bind **just any ligand.**

Applicants have amended claim 1 to recite binding activity in the specific form of "transition metal ion- or plasminogen-binding activity" in place of "ligand binding activity". Support can be found, for example, in the specification at page 16, lines 13-21 which reads (emphasis added):

> A preferred composition is, or comprises, a biologically active **peptide of HPRG** characterized in that it possesses the binding and/or biological activity of HPRG. Such binding is to a ligand that is preferably a member of the **following ligand classes**:
> (1) ligands belonging to the coagulation/fibrinolysis systems such as heparin, **plasminogen**, fibrinogen, vitronectin and thrombospondin. HPRG may bind similarly to other molecules that interact with these ligands. Thus, the present invention preferably includes novel any molecule that binds to the above-mentioned ligands.
> (2) small ligands, such as heme or **transition metal ions (zinc, copper and nickel)**, or
> (3) cells such as T cells, macrophages and platelets.

In view of this amendment, the Examiner is requested to withdraw this ground for rejection.

(3) With respect to newly added claims 56-57, the Office asserted that the specification at page 16, line 26 does not support the claimed polypeptides or peptides, which are N-terminal fragments of the human H/P domain that consist essentially of residues 350 to 408 in human HPRG or N-terminal fragments of the rabbit H/P domain that consists essentially of residues 328 to 405 in rabbit HPRG or in the case of newly added claim 57 has the sequence of residues 380 to 408 of human HPRG. These claims have been cancelled without prejudice or disclaimer.

III. Rejection Under § 102

Claims 1-2, 11, 13 and 49 were rejected under 35 USC 102(b) as being anticipated by Borza *et al.* (Biochemistry, 35:1925-1934, 1996) as evidenced by Donate *et al.* (Cancer Research, 64(16):5812-5817, 15 August 2004). As characterized by the Office, the claims are drawn to anti-angiogenic polypeptide or peptide having the sequence of the histidine-proline rich (H/P) domain of human histidine-proline rich glycoprotein (HPRG) (SEQ ID NO:5) or the H/P domain of rabbit HPRG (i.e., SEQ ID NO:6) or conservative amino acid substitution variants of SEQ ID NO's: 5 or 6, or a pentapeptide consensus sequence from said H/P domain having the sequence (His/Pro)-(His/Pro)-Pro-His-Gly (SEQ ID NO:7) or addition variant thereof having an additional 1 to 4 amino acids selected from His, Pro or Gly at the N- or C-terminus of the pentapeptide, wherein the polypeptide is not human HPRG (SEQ ID NO: 1) or rabbit HPRG (SEQ ID NO:3) (*i.e.,* not the full-length HPRG). Further, the claims are drawn to an anti-angiogenic pharmaceutical composition comprising the H/P domain of the human or rabbit HPRG polypeptide or the pentapeptide of SEQ ID NO:7 and a pharmaceutically acceptable carrier and said pharmaceutical composition is in a form suitable for injection and an affinity ligand useful for binding to or isolating an HPRG-binding molecule comprising the polypeptide or peptide of claim 1 or 2 immobilized on a solid support or carrier.

The H/P domain of human and rabbit HPRG as taught by Borza *et al.* is a polypeptide "having" the sequence of the H/P domain of human and rabbit HPRG that is not the full-length human HPRG or rabbit HPRG.

Applicants believe that their narrowing of claims 1 and 2, and, as a result, all subsequent dependent claims directed to pharmaceutical compositions, diagnostic compositions, and an affinity ligand, distinguish these claims from the cited reference. Withdrawal of this ground for rejection is respectfully requested.

IV. Rejection Under § 103

Claims 1-2, 5, 7-15 and 49 were rejected under 35 U.S.C. 103(a) as being unpatentable over Borza *et al.* (*supra*) in view of Azizkhan *et al.* (*J. Exp. Med.*. 152(4):931-944, 1 October 1980) and Simantov *et al.* (US 2001/0041670 A1, 12/6/1999, cited previously). In the words of the Office, Claims 5, 7-10, 12 and 14-15 are drawn to a diagnostically and therapeutically labeled anti-angiogenic polypeptide or peptide comprising the H/P domain of the human or rabbit HPRG

polypeptide (SEQ ID Nos:5 or 6, respectively) or the pentapeptide of SEQ ID NO:7, and a diagnostically acceptable carrier and a therapeutic anti-angiogenic pharmaceutical composition comprising said H/P domain of the human or rabbit HPRG polypeptide or the pentapeptide of SEQ ID NO:7, which is bound to a therapeutically active moiety and a pharmaceutically acceptable carrier. Borza *et al.* does not teach diagnostically or therapeutically labeled H/P domain of human or rabbit HPRG and a diagnostically or pharmaceutically acceptable carrier in suitable form for injection and wherein the label is selected from the labels recited in claims 8-10 and 15. The Office asserts that these deficiencies are "made-up for" by Azizkhan *et al.* and Simantov *et al.*

Azizkhan *et al.* teach that heparin secreted by mast cells stimulates capillary endothelial cell migration (an important component of angiogenesis *in vivo*) and the migratory activity of heparin was blocked by heparin specific antagonists (entire document, particularly abstract).

Simantov *et al.* teaches pharmaceutical compositions comprising an HPRG polypeptide and a pharmaceutically acceptable carrier (also interpreted as a diagnostically acceptable carrier) and various diagnostic and therapeutic labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others.

According to the Office, it would have been *prima facie* obvious to have produced compositions comprising diagnostically or therapeutically labeled human or rabbit H/P domains of HPRG taught by Borza *et al.* to block heparin stimulated capillary endothelial cell migration (*i.e.*, angiogenesis) in view of the teachings of Azizkhan *et al.* and Simantov *et al.* One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced compositions comprising diagnostically or therapeutically labeled human or rabbit H/P domains of HPRG taught by Borza *et al.* to block heparin stimulated capillary endothelial cell migration (*i.e.*, angiogenesis) in view of the teachings of Azizkhan *et al.* and Simantov *et al.*. According to the Office, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have diagnostically or therapeutically labeled the H/P domains of Borza *et al.* with the diagnostic and therapeutic labels taught by Simantov *et al.* to detect secreted heparin as an angiogenesis marker or to block the migratory activity of heparin and hence, angiogenesis or migration of capillary endothelial cells. Further, one of ordinary skill in the art would have been motivated to combine the diagnostically/therapeutically labeled H/P domain of human or rabbit HPRG with a pharmaceutically acceptable carrier to facilitate therapeutic administration of the labeled polypeptides. Thus, it would have been obvious

to one skilled in the art at the time the invention was made to have produced compositions comprising diagnostically or therapeutically labeled human or rabbit H/P domains of HPRG taught by Borza *et al.* to block heparin stimulated capillary endothelial cell migration (*i.e.,* angiogenesis) in view of the teachings of Azizkhan *et al.* and Simantov *et al.*.

The pharmaceutical composition (whether therapeutic or diagnostic) claims all depend from claims 1 and 2. These claims have been narrowed significantly to distinguish from Borza. As the presently claimed compositions are free of Borza (*supra*) they should also be free of any obviousness rejection based on the cited combinations with Borza. In view of the Applicants' amendment of claim 1 and 2, it is believed that the rejected dependent claims are now patentable.

V. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are free of the cited prior art, in compliance with 35 U.S.C. § 112, and therefore in condition for allowance, and respectfully requests early notice of such favorable action.

If in the Office's view, the claims are not free of the cited art, Examiner Blanchard is respectfully requested to contact the undersigned at (202) 496-7845 to see if this can be remedied rapidly, for example by either Applicants' or Examiner's Amendment.

If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. § 1.136, and any additional fees required under 37 C.F.R. § 1.136 for any necessary extension of time, or any other fees required to complete the filing of this response, may be charged to Deposit Account No. 50-0911. Please credit any overpayment to deposit Account No. 50-0911.

Respectfully submitted,

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